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Chapter 17.
DRUGS AND THE RESPIRATORY SYSTEM

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In this section, initially the drugs for bronchial asthma and Chronic Obstructive Pulmonary Disease (COPD) are considered. This is followed by a discussion of expectorants, mucolytics, drugs for cough and oxygen, and then of the drugs for rhinitis and rhinorrhea. Finally, drugs for smoking cessation are considered as smoking cessation would prevent much respiratory illness.

17.1. Drugs for bronchial asthma and Chronic Obstructive Pulmonary Disease (COPD)

17.1.1 Introduction to asthma

The **symptoms** of bronchial asthma are coughing, wheezing, shortness of breath, and chest tightness. Asthma remains a significant health problem in Australia, with prevalence and death rates that are high by international standards despite declines-Asthma affects more than 1 in 10 Australians - equivalent to over 2 million people and in 2008, 447 Australians died from asthma. The reason for the high prevalence of asthma in Australia is not known

There are more **paediatric hospital admissions** for asthma than for any other cause.

What is bronchial asthma? Bronchial asthma is an **inflammatory disease** with increased airway thickness, increased number of inflammatory cells, inflammation, bronchial hyper-reactivity and bronchoconstriction. Bronchial hyper-reactivity is cough and wheeze in response to stimuli (such as strong odours, cold air, pollutants and histamine) that would not provoke such a response in normal subjects. Some asthma is **allergic**. In severe asthma, 50-80% of this has an allergic component. In allergic asthma immunoglobulin E (IgE) plays an important part in the inflammatory cascade, and a logical way to treat allergic asthma is to prevent the effects of IgE.

The increased number of inflammatory cells in bronchial asthma occurs under basal conditions and with the presence of allergen. As there are many mediators involved in inflammatory processes, targeting one mediator is not always successful. For instance, histamine is a mediator of inflammation, but histamine acting at histamine H_1-receptors only has a minor role in bronchial asthma. Consequently, the anti-histamines (histamine H_1-receptor antagonists) are ineffective in the treatment of asthma.

Leukotrienes, cytokines and other mediators have a major role in bronchial asthma. Drugs that target only one of the inflammatory mediators are not fully effective in inflammation. Thus, **drugs that target more than one inflammatory mediator** have a major role in treating the inflammation of asthma. Asthma is usually a short-term impairment in respiration, whereas Chronic Obstructive Pulmonary Disease (COPD) is long-term impairment in respiration, and can be permanent.

17.1.2 Introduction to COPD

COPD is associated with **chronic bronchitis** and in the later stages, **emphysema**. In **chronic bronchitis** there is excessive production of **sputum, breathlessness and cough**. In **chronic bronchitis**, there is alveolar hypoventilation, hypercapnia and hypoxia. There is also an

airway narrowing and mucus plug, and the mucus plugs provide an environment suitable for secondary infection.

In **emphysema**, there is a permanent, destructive enlargement of air spaces distal to the terminal bronchiole. There is progressive airflow limitation largely due to enzymatic destruction of elastin fibres in the lung parenchyma.

COPD occurs mainly in **smokers**, develops over years with a progressive decline in lung function. COPD is the fourth leading cause of death in the US, and the leading cause of preventable death. Smoking cessation is the only intervention that has been shown to slow decline in pulmonary function, and the drug interventions to promote smoking cessation are discussed in Chapter 35. Unfortunately, only 20-40% of COPD patients quit smoking.

17.1.3 Drug delivery by inhalation

Unfortunately, with inhalation, not all the drug goes to the lungs. For instance, it has been shown that if an aerosol is used to deliver particles of 1-5 μm, after inhalation, only 10% of the drug ends up in the lungs to have its beneficial effect. The rest of the drug, 90% is swallowed, and has the potential to be absorbed, circulated and to cause adverse effects. This means that when drugs are designed for inhalation, it is still necessary to prevent systemic effects, if possible. One approach is to limit the absorption from the gastrointestinal tract. Another approach is to have a drug that is metabolised in the gut or undergoes extensive first pass liver metabolism. Both of these approaches are used with glucocorticoids, where it important to limit access to the circulation, and systemic adverse effects.

17.1.4 Drugs to treat

17.1.4.1 β_2-adrenoceptor agonists

Adrenaline is a hormone released from adrenal medulla that has widespread effects including stimulating bronchial β_2-adrenoceptors to induce bronchodilation via cell-signaling involving adenylate cyclase. **Salbutamol** is a short-acting and **salmeterol** is a long-acting selective β_2-adrenoceptors agonist. Both salbutamol and salmeterol stimulate β_2-adrenoceptors to cause relaxation of bronchial smooth muscle, and both are used clinically as bronchodilators in asthma, but they are used in different ways.

Salbutamol is a short acting selective β_2-adrenoceptor agonist, which is inhaled for the **symptomatic** relief of an asthma attack (dyspnea - shortness of breath) on an as needed basis. Thus, it is only used when an attack of asthma occurs, and salbutamol is quick acting. There is an onset of action within a few minutes, and the bronchodilation continues for 3-4 hours. In the emergency treatment of asthma, it may be necessary to use doses of salbutamol that are higher than in the normal salbutamol inhaler. Thus, in the emergency treatment of asthma, salbutamol can be delivered in a nebuliser. **Nebulisers** produce fine droplets in the air (aerosol), and are used to deliver large doses of drugs (in this case, salbutamol) in an emergency.

When the symptoms of asthma become persistent, subjects are not being managed well with salbutamol alone, and the treatment has to be re-evaluated and **prophylactic** (preventative) treatment may be indicated. **Salmeterol** is a long lasting selective β_2-adrenoceptor agonist (LABA). It is used as a chronic regular inhalation for a prophylactic effect in asthma i.e. ongoing bronchodilation to prevent an asthma attack. Salmeterol has a slow onset of action, which makes it unsuitable for use in acute attacks of asthma. Salmeterol has a duration of action of greater than 12 hours, and is usually used as an inhalation, either once or twice a

day. It has been shown that the chronic use of salmeterol improves lung function, decreases asthma symptoms, decreases nocturnal asthma and also decreases the use of short acting β_2-adrenoceptor agonists. Thus, asthmatics continue to carry their salbutamol inhalers for use in asthma attacks, but when they are taking salmeterol, there are less asthma attacks, and less use of short acting β_2- adrenoceptor agonists.

However, **long term use of salmeterol** is associated with increased risk of asthma exacerbations and death. Thus, it is not introduced into the treatment of asthma, unless it has been shown that a maximum dose of glucocorticoid is ineffective alone. If the maximum dose of glucocorticoid alone does not prevent exacerbation, salmeterol may be introduced, as in this situation the benefits of salmeterol outweighs the risks of salmeterol. Salmeterol is used in combination with a glucocorticoid in a single inhaler, as use of a single inhaler improves adherence to the asthma medicine, and the control of the asthma.

As both salbutamol and salmeterol are β_2-adrenoceptor selective, not specific, the side effects of high doses included **β_1-adrenoceptor mediated increase in heart rate,** sometimes leading to **cardiac arrhythmias.** β_2-Adrenoceptor agonists are used in the treatment of COPD, but their beneficial effect is marginal.

17.1.4.2 Muscarinic receptor antagonists

Ipratropium bromide (discussed previously in Chapter 14.4) and **tiotropium** are muscarinic receptor antagonists used in the treatment of asthma. The main advantage ipratropium has over other anti-muscarinics (e.g. atropine) is limited absorption and, therefore, limited systemic side effects. The mechanism of action of ipratropium and of tiotropium is as non-selective muscarinic receptor antagonists, which prevents acetylcholine from stimulating muscarinic receptors and causing bronchoconstriction. Effectively, the action observed with ipratropium/tiotropium is relaxation of smooth muscle. Tiotropium has a longer half-life than ipratropium and only requires once a day dosing. Ipratropium and tiotropium are occasionally used as bronchodilators in asthma. They are sometimes used in combination with a β_2-adrenoceptor agonist to give an additive effect. The muscarinic receptor antagonists can also be used with glucocorticoids as alternatives to β_2-adrenoceptor agonists

17.1.4.3 Leukotriene Receptor antagonists

Montelukast is a **leukotriene receptor antagonist** that is used in the prevention of asthma. It antagonises the LTC_4, LTD_4, and LTE_4 receptors to reduce bronchoconstriction and inflammation.

17.1.4.4 Theophylline

Theophylline was discussed in eChapter 3. Theophylline is a phosphodiesterase inhibitor. As a result of inhibiting phosphodiesterase, theophylline causes an increase in the levels of cAMP in the bronchial smooth muscle. The levels of cAMP determine the degree of bronchodilation, and when the levels are increased, there is an increased relaxation of smooth muscle. By inhibiting phosphodiesterase, theophylline inhibits the breakdown of cAMP, to cause an increased bronchodilation Theophylline is used clinically as a bronchodilator, mainly in the emergency treatment of asthma, especially when asthma is continuing despite the use of a β_2-adrenoceptor agonist.

17.1.4.5 Oxygen for COPD

In severe COPD, there is persistent hypoxemia (low levels of circulating oxygen). The obvious way to overcome this is to give oxygen at high levels than in atmosphere. Thus, in

severe COPD, there is home use of oxygen for up to 18 hours a day, and this includes sleep time. The oxygen is usually administered by a nasal cannula i.e. cannula up the nose. Low concentrations of oxygen are required, as subjects with COPD have high concentrations of carbon dioxide, and if these are further increased they may develop hypercapnia (carbon dioxide poisoning).

17.1.5 Drugs to prevent asthma

1.5.1 Glucocorticoids

The glucocorticoids have been previously discussed as drugs that have effects mediated by intracellular receptors (eChapter 3). The endogenous and synthetic glucocorticoids readily get into the cytoplasm of all cells, but only some of the cells have receptors for the glucocorticoids. When the glucocorticoid is bound to the receptor, it moves to the nucleus, and protein synthesis is initiated. Some of the proteins synthesized have anti-inflammatory actions.

There are many components to inflammation including the synthesis of prostaglandins, leukotrienes, cytokines, adhesion molecules and the release of histamine and leukotrienes, and all of these components are inhibited by the glucocorticoids. The glucocorticoids commonly used in asthma include **beclomethasone** and **budesonide**. All are inhaled. One problem with inhalation is that the glucocorticoid deposited in the mouth can lead to reduced immunity, and candidiasis (thrush) can develop. This can be minimised by using a spacer and by washing out the mouth and throat after using a glucocorticoid inhaler. The glucocorticoids are prophylactic (preventative) in the treatment of asthma. They cause an improvement in symptoms, so that there are less attacks of asthma, and this can be demonstrated by a reduced use of short-acting β-adrenoceptor agonists in subjects that take prophylactic glucocorticoids.

As drug delivery by inhalation, not only delivers drug to the lungs, but also to the gastrointestinal tract, the glucocorticoids for asthma have been designed to limit systemic effects. Thus, beclomethasone crosses membranes poorly, which means it has limited absorption from gastro-intestinal tract, and limited systemic side effects budesonide is well absorbed from the gastrointestinal tract, but have extensive first pass liver metabolism, which limits access to the circulation and decreases the risk of systemic side effects.

When there are acute exacerbations of asthma, it may be necessary to use systemic **prednisone** to overcome asthma. Prednisone is more potent than beclomethasone or budesonide as an anti-inflammatory. However, the systemic use of prednisone must be short-term use to prevent systemic adverse effects.

Glucocorticoids are also used in the treatment of **COPD**, where they give only a little benefit. Nevertheless they are used as there are no medicines that give a major benefit in COPD.

In addition to being anti-inflammatory agents, the endogenous glucocorticoids have lots of other effects in the body, and these are mimicked or exaggerated by the more potent glucocorticoids used as medicines. Administered glucocorticoids mimic the endogenous glucocorticoids to turn off the **hypothalamus-pituitary-adrenal axis**. With the long term systemic use (Table 17.1), the administration of systemic glucocorticoids causes suppression of the axis, which is slow to reverse. Thus, after long term systemic use, glucocorticoids have to be withdrawn slowly or there will be major problems due to the lack of the

endogenous compounds produced by the axis. This means that even if there are severe detrimental effects, which there can be with the glucocorticoids, they cannot be withdrawn immediately. With the inhalation of beclomethasone or budesonide, or the short-term use of oral prednisone, there is no suppression of the hypothalamus-pituitary-adrenal axis. However, this can occur if high doses of the inhaled glucocorticoids are used.

Most people with asthma take a glucocorticoid to prevent the inflammatory component of asthma and a long acting β-adrenoceptor agonist (LABA). For ease of use, salmeterol is often used in combination with a glucocorticoid in a single inhaler. Using one inhaler for both the glucocorticoid and LABA, instead of two inhalers, increases the adherence to the medication, and reduces the exacerbations of asthma.

	LONG-TERM SYSTEMIC USE	INHALATION OF BECLOMETHASONE OR BUDESONIDE; SHORT-TERM SYSTEMIC USE OF PREDNISONE
HYPOTHALAMUS-PITUITARY-ADRENAL AXIS	SUPPRESSION; PREVENTS RAPID WITHDRAWAL	NO RISK, UNLESS HIGH DOSES ARE USED FOR LONG PERIODS
GROWTH RETARDATION IN CHILDREN	COMMON	NO EFFECT
BONE RESORPTION	OSTEOPOROSIS AND OESTEONECROSIS	MODEST
CARBOHYDRATE AND LIPID METABOLISM	HYPERGLYCEMIA, FAT REDISTRIBUTION	MINOR
CATARACTS	WELL-ESTABLISHED	UNPROVEN
SKIN THINNING	COMMON	NO RISK, UNLESS HIGH DOSES ARE USED FOR LONG PERIODS

Table 17.1 Adverse effects with glucocorticoids

With long term systemic used of glucocorticoids, **growth retardation in children may occur**, but this has not been reported with inhalation of glucocorticoids. The glucocorticoids promote **bone resorption**, and this leads to osteoporosis (thinning of the bone) and osteonecrosis (breakdown of bone). Osteoporosis is observed with the long term systemic used of glucocorticoids, but is relative modest with inhalation or short term use of the glucocorticoids. The glucocorticoids have major effects on both carbohydrate and lipid **metabolism** leading to hyperglycaemia and fat redistribution. This is a major problem with the systemic long term use of glucocorticoids but only a minor problem with inhaled or short term use of oral glucocorticoids. Long term glucocorticoid use is associated with **cataracts**, but this is unproven with inhaled or short term use of oral glucocorticoids. Systemically administered glucocorticoids cause **skin thinning**, but this is only observed with long term use of high doses of inhaled steroids.

17.1.5.2 Cromolyn sodium

The other drugs used to prevent asthma are the mast cell stabilisers including **cromolyn sodium**. The exact mechanism of action of cromolyn sodium is unknown, but it is known that it leads to an inhibition of mediator release from mast cells, and these mediators include the

bronchoconstrictors **histamine** and **leukotrienes**. Cromolyn sodium is taken by inhalation. As it is poorly absorbed from gastrointestinal tract, side effects are rare with cromolyn sodium. Cromolyn sodium is used to prevent an asthma attack, but is not useful in an asthma attack, when the mediators have been already been released. With regular use, cromolyn sodium can prevent asthma due to antigenic or exercise challenge, and can decrease bronchial hyper-reactivity.

17.1.6 Combination treatment to treat and prevent asthma

Formoterol is a rapidly acting selective β_2-adrenoceptor, which is used in combination with the glucocorticoid budesonide for the treatment and prevention of asthma. Formoterol causes a rapid bronchodilation to relieve the symptoms of asthma, whereas budesonide reduces the inflammation.

17.1.7 Drug for allergic asthma – omalizumab

Moderate-to-severe allergic asthma is treated with inhaled glucocorticoids. If this does not control the asthma, and there is an allergic component, immunotherapy may be tried. **Omalizumab** is a monoclonal antibody to immunoglobulin E (IgE). Omalizumab combines with IgE to prevent its actions. Thus, omalizumab prevent IgE from promoting mast cell degranulation (release of histamine, leukotrienes etc). This, in turn, reduces the immune response to the allergen to decrease the symptoms of asthma. Omalizumab is not active after oral administration, and is administered subcutanously.

17.1.7 Emergency treatment of asthma

When subjects with asthma are taken to the emergency department of the local hospital, the initial treatment is usually high dose salbutamol delivered by nebulizer. If this does not give enough bronchodilation, theophylline may be administered to increase the bronchodilation. In severe exacerbations of asthma, intravenous glucocorticoids are used, and it is usually the potent glucocorticoid prednisone.

In the ambulance, in severe asthma high dose salbutamol may delivered by nebulizer or, if that is not possible, intravenously. In severe asthma, intravenous glucocorticoid may be given by the paramedic. The glucocorticoid used for this is a relatively weak glucocorticoid – hydrocortisone.

17.2. Expectorants, mucolytics, cough, oxygen and entonox

17.2.1 Introduction to expectorants and mucolytics

Expectorants remove sputum while **mucolytics** thin mucus. Expectorants and mucolytics are used in the treatment of bronchitis associated with smoking/COPD. Expectorants and mucolytics are also used in the treatment of cystic fibrosis.

Cystic fibrosis is a genetic disorder that affects airways and ducts in lungs, pancreas and sweat glands. In cystic fibrosis, thick and viscous secretions are produced in ducted organs (lungs, pancreas and sweat glands). With these increased secretions, there is an increased risk of respiratory infection. The frequent and persistent lung infections associated with cystic fibrosis leads to irreversible lung damage (**bronchiectasis**).

17.2.2 Expectorants

Expectorants aid in removal of sputum from the bronchial passages. The most common used expectorant is **water**, which is taken as steam from hot water in a basin or in a nebuliser. The medicine used most commonly to remove sputum is the muscarinic receptor antagonist **ipratropium bromide**, which is administered by inhalation. Both of these agents, water and ipratropium bromide act by thinning secretions and thereby keeping airways and organ ducts patent (open). This is an effective way of combating opportunistic infections.

17.2.3 Mucolytics

Mucolytics are agents that thin viscous mucus. The most commonly used of these is **acetylcysteine**, which breaks disulphide bonds that pack the mucin molecule, and this thins the viscous mucus. Acetylcysteine is administered in a nebuliser or using an intratracheal tube.

17.2.4 Cough

A cough is a physiological mechanism to clear respiratory passages of foreign material and excessive secretions. Thus, when something is irritating the bronchial mucosa this leads to bronchoconstriction, and the bronchoconstriction stretches the **respiratory stretch receptors**, which are also known as the cough receptors (Figure 17.1). The stretch receptors send a message to central nervous system and there is a reflex cough to clear the substance causing the irritation.

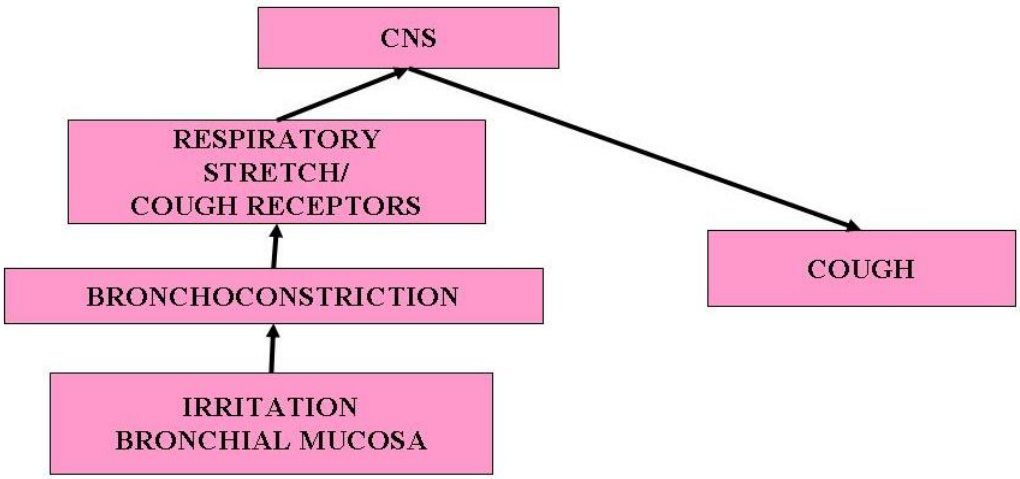

Figure 17.1 The cough reflex (Copyright Sheila Doggrell, QUT)

Thus, a cough performs a useful physiological function, and it is only when cough is chronic and/or unproductive that it becomes annoying and fatiguing.

An **anti-tussive** is an agent used to relieve or prevent a cough. For the cough associated with bronchial asthma, the **selective β_2-adrenoceptor agonists (e.g. salbutamol)** are used. Salbutamol causes bronchodilation to reduce the stimulation of the respiratory stretch receptors. **Menthol** vapour also reduces the sensitivity of the respiratory peripheral stretch/cough receptors.

There are also centrally acting anti-tussive agents including **codeine** and **dextromethorphan**. Codeine is analgesic and anti-tussive. **Methorphan** is an analog of codeine. The L-isomer of methorphan is analgesic and addictive. The D-isomer of methorphan (dextromethorphan)

is not analgesic or addictive, but is anti-tussive. Thus, dextromethorphan is the agent used to prevent cough.

17.2.5 Oxygen

Oxygen gas can be considered as a medicine. Under certain circumstances, oxygen gas is a very effective medicine. It is used in **hypoxic hypoxia** e.g. airway obstruction, where lack of respiration is the cause of the lack of oxygen. Oxygen gas is also used in **ischemic hypoxia**, where there is a lack of supply of oxygen and nutrients supplied by the blood vessels e.g. atherosclerosis and thromboembolism. Oxygen gas can be administered either by inhalation with catheters up the nose, or using a mask that covers nose and mouth. Low concentration are used in COPD, as the levels of carbon dioxide are high, but when the levels of carbon dioxide are low, higher concentration can and are used to treat hypoxic hypoxia and ischemic hypoxia

12.2.6 Entonox

Entonox is a mixture of 50% oxygen and 50% of nitrous oxide. It is commonly known as laughing gas. Entonox is a self-administered anaesthetic in child birth. ~~On~~ In(?) the ambulance, entonox is used for pain relief, but it only has a relative low ability to relieve pain.

17.3. Drugs for rhinitis and rhinorrhea

17.3.1 Introducton

Rhinitis is the acute or chronic inflammation of the nasal mucosa causing itching and sneezing. Rhinorrhea is excessive watery nasal secretions (a runny nose). Rhinitis and rhinorrhea are caused by either viral infections (e.g. the common cold) or allergic reactions, such as seasonal allergies (e.g. hayfever) or chronic/perennial allergies (e.g. dust mites, animal dander). Allergic rhinitis is suffered from by 1 in 5 people and this affects their quality of life, and reduces school and work performance. Unlike in the allergic condition asthma, where histamine only has a minor role, histamine is a major mediator of rhinitis. **Histamine H_1-receptor antagonists** counter the rhinitis.

In rhinitis there is nasal vasodilation and increased blood vessel permeability (oedema) leading to an enlargement of nasal mucosa, which causes difficulty with inspiration of air (difficulty breathing through the nose). Activation of the sympathetic nervous system causes vasoconstriction in the nasal mucosa, decreases blood vessel permeability, which in turn reduces the nasal mucosa size, and improves the ability to inspire through the nose. Thus, **sympathomimetics** are useful in nasal rhinitis and congestion

17.3.2 Histamine and H_1-receptor antagonists

Histamine has a major role in allergic rhinitis. In the presence of an allergen, the mast cells in the nasal mucosa degranulate to release histamine which actions on the histamine H_1-receptors on the endothelial cell lining of blood vessels to cause contraction of these cells, which increases the space between these cells (Figure 17.2). Fluid and proteins can then move out of the blood vessels to form oedema. This leads to inflammation of the nasal mucosa, which is partly due to the oedema.

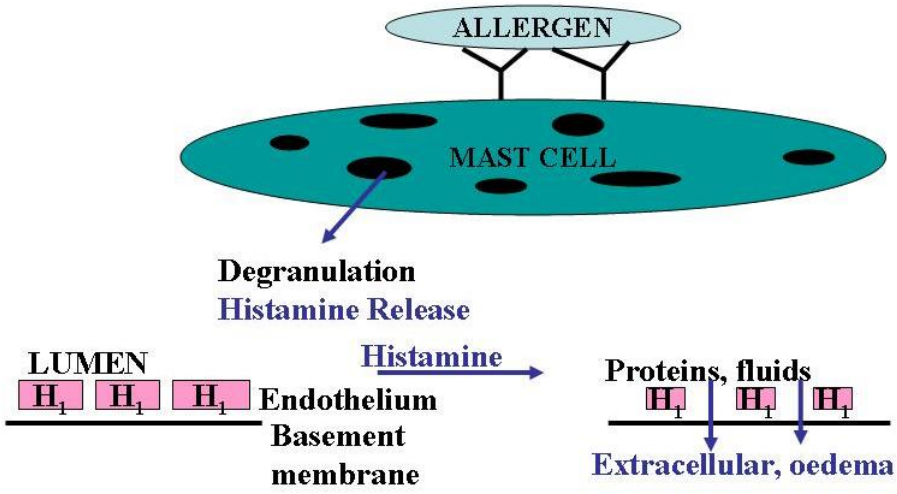

Figure 17.2 Histamine and allergy (Copyright Sheila Doggrell, QUT)

The H_1-receptor antagonist **fexofenadine** is used in the treatment of nasal allergy. It is active after oral administration. Fexofenadine cause suppression of the symptoms in rhinitis and rhinorrhea. It is most effective at the beginning of the hayfever/pollen season when pollen counts are low. When pollen counts get high, there are mediators other than histamine involved in the allergic reaction, and the anti-histamines are ineffective against mediators other than histamine. These newer histamine H_1-receptors antagonists do not get into the central nervous system and therefore cause little or no sedation.

17.3.3 Sympathomimetic

The sympathomimetic most commonly used in rhinitis/rhinorrhea is **ephedrine**, which is also known as pseudoephedrine. Ephedrine, as discussed in the Chapter on the sympathetic nervous system, is a **mixed acting amine**, which means it has both direct and indirect effects at adrenoceptors. The **direct action** is that ephedrine is a weak agonist at α- and β-adrenoceptors. The **indirect action** is that ephedrine releases noradrenaline, which in turn stimulates the α- and β- adrenoceptors.

Ephedrine is active after oral administration, and after oral administration it causes an α-adrenoceptor-mediated vasoconstriction, which overcomes the nasal decongestant. After oral administration, ephedrine also causes a β_2-adrenoceptor-mediated bronchodilation, which is useful in bronchial congestion, which often occurs with nasal congestion. In addition to being active after oral administration, ephedrine can be applied topically to the nasal mucosa in a nasal spray. With topical administration, this limits the effects to the nose. Topical administration limits adverse effects, but also reduces the beneficial bronchodilation. After oral administration, the adverse effects observed with ephedrine include central nervous system stimulation, and sympathomimetic actions such as an increased heart rate (tachycardia) and an increased blood pressure.

17.3.4 Muscarinic receptor antagonist

Ipratropium bromide is the antimuscarinic agent used in the treatment of rhinorrhea. It is used in the form of a nasal spray. In the nose, ipratropium dries up the nasal secretions. The highest concentrations of ipratropium are in the nose, and there is limited absorption, and a low incidence of adverse effects with this route of administration.

17.3.5 Cromolyn sodium

In addition to taking agents such as the H_1-receptor antagonists and the sympathomimetic ephedrine during rhinitis and rhinorrhea, there are medicines available to prevent these conditions. The mast cells stabiliser **cromolyn sodium** is available as a nasal spray. Cromolyn sodium has to be taken as prophylaxis (prevention) from before the start of the allergy season, and then it will both reduce the symptoms and improve the quality of life in people with rhinitis and rhinorrhea.

17.3.6 Glucocorticoids

The most effective preventatives for the treatment of rhinitis and rhinorrhea are the glucocorticoids. The glucocorticoids **beclomethasone** and **budesonide** are available in nasal sprays. With the use of these glucocorticoids in nasal sprays, there are no systemic side effects. At the peak of the hayfever season, the glucocorticoids are more effective than the antihistamines, as histamine is not the only mediator of the allergy/inflammation.